Clinical-Pathological Conference*

A 36-year-old Filipino farm laborer was admitted to the Santa Barbara General Hospital with a complaint of pain in right chest.

Present Illness: The patient developed a severe "cold" four weeks before entering the hospital. This was accompanied by pain in the right side of his chest. As told by the patient, the cold was followed by pneumonia and he was admitted to another hospital because of high fever and productive cough. In that hospital he was treated with penicillin. A chest film taken at that time revealed a right pleural effusion. The fluid was aspirated with amelioration of the clinical symptoms. The temperature returned to normal but the productive cough persisted. Repeated examinations of the sputum were negative for tubercle bacilli and pathogenic fungi. Because tuberculosis was strongly suspected, the patient was transferred to the tuberculosis sanitarium at the Santa Barbara General Hospital. During this time he had lost 15 pounds.

Past History: The patient had always enjoyed good health and there was no pertinent medical or surgical history. He had been a resident of Santa Barbara County for the past 15 years, living in the Lompoc area. He had no knowledge of his diabetes prior to the hospital admission.

Family History: Father and mother deceased—cause of death not known. Three brothers were living and well.

Physical Examination: The patient was a fairly well developed, small Filipino. He was not in acute distress. There was no evidence of dyspnea. The only positive physical finding was diminished to absent breath sounds in the right lower chest posteriorly. The left chest was negative to percussion and auscultation.

Laboratory Findings: (On admission) Hb 14 grams. RBC 4,860,000; WBC 6,050; PMN 71 per cent; Lymphs 19 per cent; Eosins 10 per cent. Blood sedimentation rate, 11 mm. in one hour. Fasting blood sugar 296 mgm. per cent. Urine, albumin—trace, sugar—4 plus; Acetone and diacetic acid—negative. Serologic tests for syphilis, Kahn and Kline reactions—negative.

Radiologic examination of the chest on admission to the sanitarium revealed an area of increased density at the level of the left third rib posteriorly; the left lung parenchyma was radiographically clear. The right lung field showed evidence of cavitation at the level of the outer part of the second and third interspaces; there was a uniform dense shadow below this level which was suggestive of a fluid level.

Course in the Hospital: The patient was treated with diet and insulin therapy for control of the diabetes. After four weeks, urine sugar reactions were negative and the fasting blood sugar levels were below 100 mg. per cent. At this time 10 units of protamine zinc insulin were being given daily. His general condition appeared improved and he gained four pounds in two months. The chest symptoms completely subsided.

On July 30, 1946, approximately two months after admission to the Santa Barbara General Hospital, he began to complain of severe frontal headaches which were not associated with nasal discharge or sinus tenderness. Three 24-hour sputum specimens were examined at this time but no acid fast bacilli or other pathogenic microorganisms were seen. Chest films on July 31 showed only a small area of fibrosis at the level of the right second interspace and the radiologist suggested that if the chest lesions were caused by tuberculosis, the disease was probably in a healed state.

The headaches continued and required codeine for relief. A blood count on August 8, 1946, revealed WBC 13,500; PMN 64 per cent; Lymphs 21 per cent; Eosins 15 per cent. The patient became progressively more confused mentally and on August 12, a spinal tap was done. Pressure, 96 cm. of spinal fluid; Queckenstedt, negative. Spinal fluid sugar 57 per cent (blood sugar 190 mg. per cent). Cell count, WBC 605; PMN 10 per cent; Lymphs 90 per cent; RBC—too numerous to count. Globulin, "marked increase." Spinal fluid chlorides, 792 mg. per cent. Colloidal gold curve, 5555554331. Blood sedimentation rate, 34 mm. per hour.

The neurologic picture was not remarkable save for increasing mental retardation. The patient developed a marked tremor and urinary incontinence terminally. He expired quietly on August 18, 1946, three months after admission.

CLINICAL DISCUSSION

DR. HOBART A. REIMANN†: The case is one of about four months' duration, beginning with a "cold," followed by pleural effusion, pneumonia and cavitation of the lung. After a period of improvement and healing of the pulmonary lesion, evidence of intracranial disturbance developed about a month before death.

From the clinical records, tuberculosis was suspected, but the initial recovery was more rapid than one would expect if it had been tuberculosis pneumonia; tubercle bacilli were never found, there was

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eosinophilia and the sedimentation rate was not increased. If it were tuberculosis, the final state could have been interpreted as tuberculous meningitis or cerebral tuberculoma, but of which there was no diagnostic evidence. Fever is not mentioned after the early period in the description of the case, nor is the character of the sputum or the pleural effusion noted.

The history also suggests the possibility of viral pneumonia, followed, after too long an interval, however, by encephalitis. The pleural effusion, cavitation and eosinophilia do not favor this diagnosis.

Pulmonary abscess may have been considered because of the evidence of pneumonia followed by pleural effusion and cavitation. The cerebral symptoms could be explained by metastatic abscess in the brain. A "cold," on rare occasions, may give rise to lung abscess, but there is no evidence in the history of the aspiration of a foreign body or of surgical operation in the nose or throat. There is no description of the sputum or of the pleural fluid.

Carcinoma of the lung and metastasis to the brain is a possibility, but again, healing of the pulmonary lesion and other laboratory evidence does not favor the suggestion.

This leaves the most likely possibility to be discussed; namely, coccidioidomycosis with terminal coccidioidal invasion of the brain. The patient was a farmer who lived in an endemic area. The disease usually begins as a "cold" and in the great majority of cases never progresses beyond that brief period. In a few instances it causes more serious disease, as in the present one, probably abetted by the coexisting diabetes. Pneumonia indistinguishable from viral pneumonia occurs, but it is more often accompanied by pleural effusion and cavitation which, as described, may heal with little or no trace. In favor of this diagnosis are the patient's occupation, the clinical course, the normal sedimentation rate and a normal leukocyte count, with eosinophilia. No mention is made in the record of any specific tests for coccidioidomycosis.

It is well known that patients with coccidioidomycosis who do not have erythema nodosum during the initial stage are more likely later to develop the generalized form. In the present case, no skin lesions were noted, the pulmonary lesion healed, but one month later cerebral symptoms appeared which ended in death in another month. This suggests that infection persisted in the lung despite the negative roentgen ray evidence, and by way of blood stream the fungus eventually reached some area in the brain, probably the basilar region, lodged there and grew. Dissemination in some patients may include many organs and the brain is involved in 25 per cent of these instances. Furthermore, and as in the case at hand, localization may take place in the brain alone. A small percentage of persons who have had coccidioidomycosis even in its mildest form, especially those in whom no skin lesion occurred at the time, are liable to develop the disseminated form as long as ten years afterward.

The clinical diagnosis of the case is pulmonary coccidioidomycosis followed by coccidioidal basilar meningitis.

PATHOLOGIST'S DISCUSSION

DR. WILLIAM O. RUSSELL‡: When I heard that Dr. Reimann was discussing this case, I was reasonably sure that he would make the correct clinical diagnosis, knowing of his interest and experience with communicable diseases. There was one thing that was not given in the clinical history that would have further assisted Dr. Reimann in making the diagnosis of coccidioidomycosis. This was the fact that the patient lived in the Lompoc area in Santa Barbara County near Camp Cook. It was from Camp Cook that the first cases of coccidioidomycosis were reported in military installations in California during the war [1] and this area is now known to be endemic for this disease.

The postmortem examination of this man disclosed dense fibrous pleural adhesions over the surfaces of the lungs and sections of the lungs revealed small discrete white foci less than 1 mm. in diameter scattered in all of the lobes. A small cavity approximately 2 cm. in diameter was present in the upper lobe of the right lung. This cavity was surrounded by a small zone of moderately firm tissue and lined by a gray white caseous appearing surface.

In the mediastinum there were several enlarged lymph nodes having central caseous foci. Small gray white nodules similar to those seen in the lungs were noted in the liver, spleen and kidneys.

The weight of the brain was remarkably increased, being 1530 grams. The subarachnoid space over the base of the brain and particularly in the region of the optic chiasm was filled with a greenish yellow exudate. This exudate extended laterally into the sylvian fissures. Examination of the leptomeninges over the cerebral hemispheres disclosed small discrete yellow foci, most frequently seen in juxtaposition to the blood vessels in the sulci. Step sections through the brain disclosed moderate dilatation of the lateral, third and fourth ventricles. Small discrete slightly elevated nodules less than 1 mm. in diameter, imparting a fine granularity to the surface, were noted on the ventricular surfaces. In the vermis of the cerebellum, extending slightly into the right lobe, a focus of indurated tissue was noted that on section showed a large central area of caseous necrosis. The indurated tissue measured 13 mm. in diameter and involved the folia and the subarachnoid space.

I should like to admit at this time that, after reviewing these gross pathologic changes without the benefit of the microscopic examination, it was my opinion this was a typical case of tuberculosis with a cavity in the lung, with miliary dissemination to the lungs, liver, kidneys and spleen, and a tuberculoma in the cerebellum with leptomeningitis. However, I would like to add, apologetically, that at that time the clinical history was not available and I did not know of

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the 10 per cent eosinophilia and that the patient lived in the Lompoc area.

Microscopic examination of the cavity in the upper lobe of the right lung, one of the enlarged lymph nodes in the mediastinum, the lesion in the cerebellum, the leptomeninges and the small gray foci in the parenchymatous organs disclosed in all instances granulomatous lesions containing spherules with double contoured capsules and frequently containing endospores characteristic of coccidioides immitis. Caseation was present but was remarkably different from what is usually seen with tuberculosis, there being a more acute type of inflammation with infiltrating polymorphonuclear leukocytes. A remarkable tendency was noted for the giant cells seen to have phagocytized the large spherules. The section taken from the cerebellum revealed the granuloma extending up to and involving the leptomeninges. This is a particularly significant fact in regard to the genesis of the leptomeningitis, since the question is posed whether the lesion in the cerebellum caused the meningitis or whether the subarachnoid space was infected from the blood. Certainly, in this case the leptomeninges could have been infected by organisms from the granuloma. It is interesting to note that, in the recently published studies of Forbus and Bestebreurtje,[2] the brain substance in coccidioidomycosis is not nearly so frequently involved as with tuberculosis. These authors concluded, therefore, that infection of the leptomeninges in coccidioidomycosis does not often result from the extension of a focus of the disease in the brain to the subarachnoid space. It was further pointed out that, because the organisms were of appropriate size to lodge within the vessels of the subarachnoid space, it was most likely that infection of the leptomeninges was by this means.

Anatomic Diagnoses: These were fibrocaseous coccidioidomycosis with cavitation in the upper lobe in the right lung; fibrocaseous coccidioidomycosis of the mediastinal lymph nodes; fibrous obliteration of the pleural cavities; miliary coccidioidomycosis of the lungs, liver, spleen and kidneys; coccidioidomycoma of the cerebellum; coccidioidomycotic leptomeningitis; granular coccidioidomycotic ependymitis; and internal hydrocephalus.

REFERENCES

1. Shelton, R. M.: Survey of coccidioidomycosis at Camp Roberts, California, J.A.M.A., 118:1186-1190 (April 4), 1942.

2. Forbus, W. D., and Bestebreurtje, A. M.: Coccidioidomycosis: a study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease. The Military Surgeon, 99:653-719, 1946.